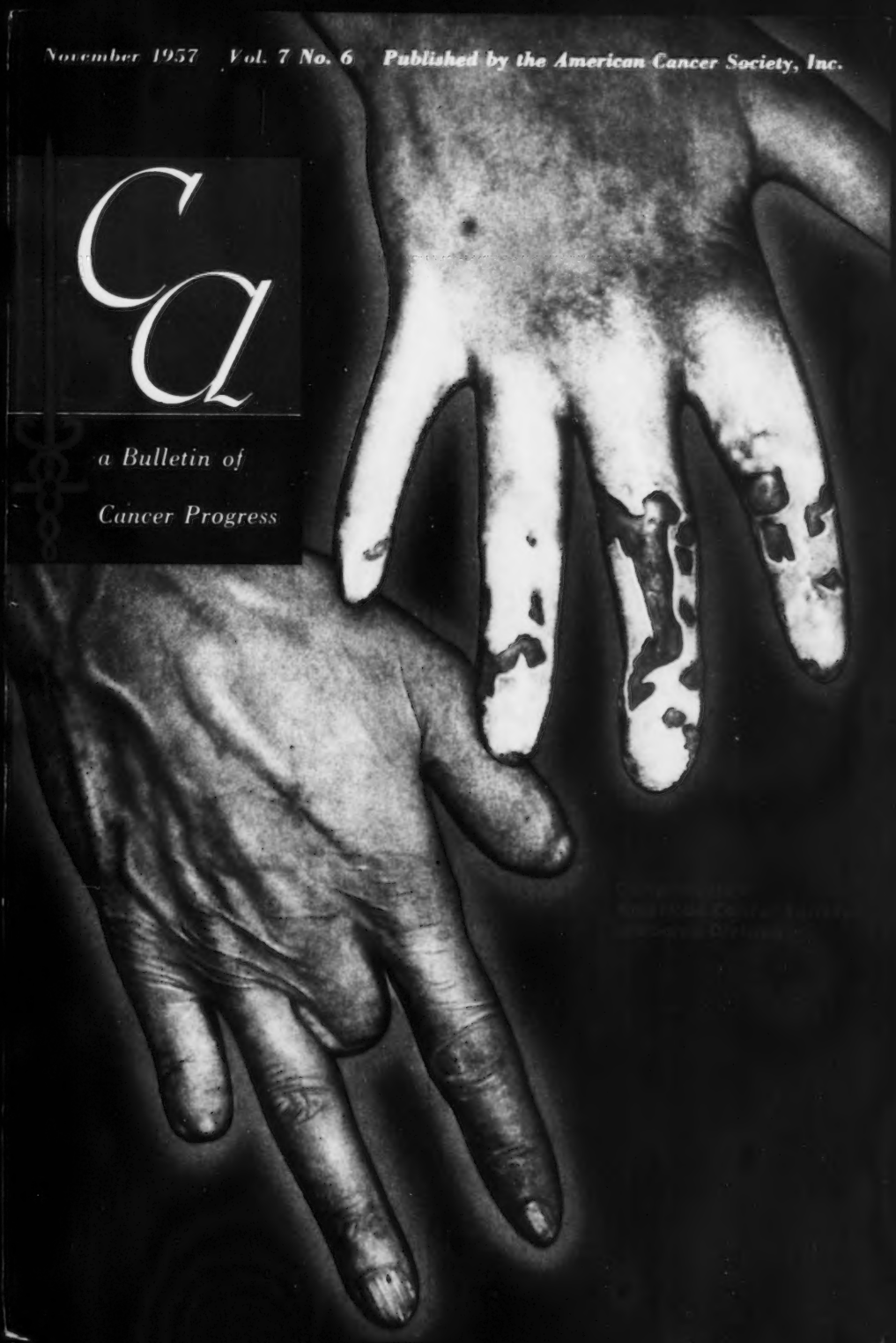
November 1957 Vol. 7 No. 6 Published by the American Cancer Society, Inc.

Ca

a Bulletin of

Cancer Progress



malignant yet benign

The high incidence of skin cancer, its curability, its unique accessibility, its low malignancy, the infrequent metastases, and the usually identifiable etiology, the ease of early diagnosis, and the encouraging prospect of prophylaxis constitute a distinct dichotomy between cancers of the skin and those of other sites.

Since skin cancers are usually preceded by obvious benign or precancerous lesions they can be prevented by frequent examinations by the family doctor, the dermatologist, and the industrial physician, by biopsy examination of all suspicious lesions, by instructions concerning prophylaxis, and by the use of protective measures. And when they do occur they can usually be cured if diagnosed early.

The complete accessibility of cancer of the skin adapts it to the study of the experimental and clinical effects of surgical, radiological, and chemotherapeutic procedures. Much of the present knowledge of carcinogenesis and of cancer etiology was gained from studies of environmental skin cancers in man and skin lesions produced experimentally in animals.

Knowledge of the carcinogenic effects of radiation was first derived from the early radium and roentgen-ray lesions of the skin. Skin cancer in animals is the commonest end point of carcinogenic studies of suspected environmental agents, including those encountered in certain occupations.

Skin cancer, then, is not an entirely unmitigated malignant curse but is being adapted to the benefit of mankind and, paradoxically, even to the benign project of the control of cancer itself.

Cover—

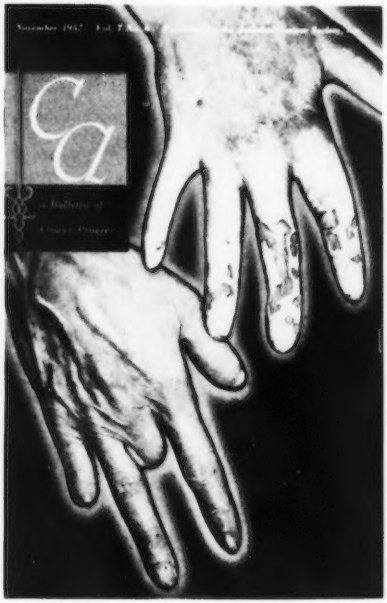
Below: Hand of the late dean of American radiology, Dr. George E. Pfahler.

Above: Hand of a young radiologist patient of Dr. Pfahler.

Dr. Pfahler died of leukemia January 29, the eighty-third anniversary of his birth. A few days before, in transmitting these photographs, he wrote: "In the early days the hand was held in front of the fluoroscope with no protection whatever. I destroyed by electrodesiccation more than two hundred and fifty precancerous lesions on my hands, and in two fingers malignant disease developed. My young radiologist patient had four fingers so badly damaged that I advised their removal. We have learned to protect ourselves now and none of our younger radiologists need suffer from this condition."

These hands illustrate the possible cancer hazard from the pioneering exposure to any new therapeutic, diagnostic, environmental, or occupational modality.

Radiation cancer, like other types with known etiology, can be prevented.



[Photographs are left hands, reversed to conform to cover format]

NEWSLETTER

NOVEMBER 1957

Advances in Leukemia: reported from the Annual Meeting of the American Association for Cancer Research. Continued from September Newsletter.

D. W. H. Barnes and J. F. Loutit (British Atomic Energy Research Establishment, Harwell) in their early experiments gave mice 1500 r over 25 hours one week after inoculating them with lymphatic leukemia. The animals are in good shape with four marrow injections for well over a year. A later series in which the animals were given 950 r (LD98) and then injected with isologous or homologous marrow from normal or leukemia-immunized animals didn't work out so well -- life was prolonged, but many animals died of delayed leukemia or wasting, a common complication of these homeografts.

John J. Trentin (Baylor) achieved similarly exciting results with a transplanted Gardner lymphosarcoma. One curious result of these experiments: Irradiated leukemic mice infused with rat marrow for long periods adopted some of the immunogenetic characteristics of the rat. Rat skin was successfully transplanted to these mice, and the transplants remained in a healthy, growing state until something (like the injection or regeneration of mouse marrow) interfered with the transplanted rat's hematopoietic system. These investigators foresaw no clinical application of these findings. Osgood (U. of Ore.) suggested that this system might work between identical twins, one of which is leukemic. Whether simple heterologous, homologous, or autologous marrow infusions (without radiation) would have affected the course of lymphatic leukemia is not known.

Kirschbaum and Kawamoto (Baylor and M. D. Anderson) have shown that urethane is coleukemogenic (with X rays) and that marrow infusions protect from the lethal effects of urethane just as they do against X rays. Their experiments were done with mice.

Other incidental intelligence on leukemia included:

Kirschbaum (Baylor and M. D. Anderson Hosp.) found that urethane potentiated the leukemogenic effects of

X rays, even to overcoming the protective properties of thigh shielding.

Friend (Sloan-Kettering Institute) reported protecting 80 per cent of mice with a formalin-inactivated leukemia virus which normally affects adult as well as newborn mice. This was described in a press release as "the first successful vaccination against cancer in mammals."

Ida, Kirschbaum, and Taylor (M. D. Anderson and Baylor) found that leukemia, which appears spontaneously in aged C3H mice, came early if newborn mice were given saline extracts of these leukemic cells or viable leukemic cells of foreign origin.

The Berliners and T. Dougherty (U. of Utah) have found profound differences in corticosteroid metabolism in normal and leukemic humans; and Van Dooren and J. H. Dougherty have observed equally curious differences in metabolism by normal bone and osteosarcoma from a radiothorium-injected beagle.

Toch (Children's Cancer Research Found., Boston) said that leukemic patients in complete hematologic remission may have the usual mild form of varicella, but in active acute leukemia varicella also becomes aggravated and requires careful management and supportive treatment.

Upton, Wolff, and Furth (Oak Ridge and Children's Cancer Research Found.) splenectomized mice one week before radiation and thereby reduced to less than one-half the resulting myeloid leukemia. The frequency of thymic lymphomas was not affected by splenectomy.

Carcinogenesis: Richardson (U. of Wash.) and Griffin and O'Neal (M. D. Anderson) fed DAF (diacetylaminofluorene) for twenty-four weeks to rats and harvested 100 per cent cirrhosis, 50 per cent hepatocarcinoma, 5 per cent bile duct carcinoma, and 10 per cent epidermoid carcinoma. But if the mice were hypophysectomized they produced 60 per cent intra-orbital, lacrimal adenocarcinoma and 10 per cent epidermoid carcinoma of the ear -- liver, adrenals, prostate, testes, and thyroid atrophied.

Riley (SKI) found that something in the melanoma (perhaps a metabolic product) protected mice against lethal doses of p-phenylene diamine.

The significant finding by Moore, Sandberg, and Schubarg (Roswell Park) that tumor cells frequently can be found in veins draining tumor areas was proposed as a potentially useful tool in analyzing the efficacy of chemotherapy. (Continued after page 216)

CA a Bulletin of Cancer Progress

Please address all correspondence to
WILLIAM H. STONER, M.D.
Executive Editor
American Cancer Society, Inc.
521 West 57 St., New York 19, N. Y.

NOVEMBER 1957 VOL. 7, NO. 6

CONTENTS

Published bimonthly by
AMERICAN CANCER SOCIETY, INC.
New York, N. Y.

Annual Subscription $2.50

Special bulk rate to organizations other than Divisions subscribing in quantities of 200 or more.

Keeping up

Smoking and Bronchial Epithelium

Changes in the tracheobronchial trees of 117 autopsied patients were studied histologically. Of this group, thirty-four had died of bronchogenic carcinoma and all were cigarette smokers. The remainder died of other causes, and sixteen had never smoked, twenty had smoked less than one pack a day, and forty-seven more than one pack a day. More than 80,000 histological examinations were made to correlate basal-cell hyperplasia, stratification, squamous metaplasia, and carcinoma in situ with the smoking habits. These epithelial changes were least frequent in the group that never smoked regularly, with a progressive increase in the moderate and heavy smokers. The most extensive changes were found in those who had died of lung cancer. These findings are fully consistent with the hypothesis that inhalants, such as certain dusts and vapors as uranium and chromate dusts, general air pollution, and cigarette smoke, are important factors in the causation of bronchogenic carcinoma. The findings are also fully consistent with the theory that cigarette smoking is an important factor in the causation of bronchogenic carcinoma.

Auerbach, O.; Gere, J. B.; Forman, J. B.; Petrick, T. G.; Smolin, H. J.; Muehsam, G. E.; Kassouny, D. V., and Stout, A. P.: Changes in the bronchial epithelium in relation to smoking and cancer of the lung; a report of progress. New England J. Med. 256:97-104, Jan. 17, 1957.

Survival in Cancer

The prognosis in cancer depends on so many factors, some still unknown, that it is seldom possible to predict the outcome in any individual case. Importance of the different factors can be assessed only by collection and analysis of large masses of data. The present study from the General Register Office, London, is concerned with the effects on survival of clinical stage of the disease at registration and of the duration of symptoms prior to registration according to the patient's statement. The following sites were selected for study: stomach, large intestine, rectum, lung and bronchus, skin, cervix, and prostate. The clinical stages were: (a) early, growth confined to organ of origin; (b) late, local extension beyond organ of origin; and (c) metastatic, to distant organs at time of registration. In gastric cancer, not only is the average symptomatic duration of the disease shorter as the severity of the condition on registration increases, but in each stage the survival rate is highest when the history is longest. Prognosis as measured by the five-year–survival rate in internal cancer is almost entirely determined by the stage the growth has reached, and it is relatively independent of the duration of symptoms, although a better prognosis is often associated with a longer history. To the contrary, epithelioma of the skin, where the very early stages of the growth are obvious, shows a definite correlation between a short history and an early stage, a shorter history being more frequently associated with a better prognosis. The rate of growth of the tumor is the most important factor influencing survival rate after radical treatment. Intrinsic malignancy of the growth is also an important factor. A rapidly occurring change arouses the patient to seek medical advice at an earlier date than does one which proceeds more slowly. The condition or extent of the growth

with Cancer

when diagnosed may be the best indication of its intrinsic malignancy. A long symptomatic history is a favorable prognostic sign, if the disease is still operable. We know but little concerning degrees of malignancy and of changes in malignancy during the course of the disease. Early diagnosis and early treatment, therefore, are still of utmost importance in the improvement of survival rates.

McKenzie, A.: Duration of symptoms, clinical staging and survival in cancer of certain sites. Brit. J. Cancer 10:401-407, Sept., 1956.

Au^{198} in Ovarian Cancer

In nine of ten cases of ovarian cancer with ascites treated intraperitoneally with radioactive colloidal gold, reaccumulation of fluid was prevented, permitting the patients to carry on their normal activities in comfort. It is recommended that this therapy be applied routinely in carcinoma of the ovary as a prophylactic measure against ascites no matter how small the tumor may seem or how completely the surgeon believes it removed. The authors suggest that the chances of prolonging life in patients with early ovarian cancer may be enhanced by the use of radioactive colloidal gold in addition to early, complete surgery and roentgen-ray therapy.

Cohen, J. S., and Sklaroff, D. M.: Intraperitoneal radioactive gold in ovarian cancer. Obst. & Gynec. 6:68-74, July, 1955.

Cancer in Animals

Cancers occurring in domesticated animals should be used to advantage in the battle against cancer in man. The incidence of neoplasia, benign and malignant, per thousand animals is approximately: dog 50, cat 10, horse and ox 1, and for pig 1 in 40,000—a rich, largely untapped source for oncologic study and research. Closer study of tumors in domesticated animals would assist in the elucidation of the cancer problem in general, and particularly in respect to etiology and therapy. For example, quite a high proportion of cancers in the cat occur in the alimentary canal, whereas cancer is uncommon in the alimentary canal of herbivora. And the high frequency of esophageal and glossal cancers in cats suggests the possibility that milk may contain a carcinogenic substance. Again, if a study were in progress concerning the distribution of certain substances in tumors, fresh material, neoplastic and normal, is available in large quantities in the domesticated animals. No agency has been set up for recording statistics in respect to cancer of animals; the best information available is imperfect estimates based on operation, post-mortem, and abattoir data. The differences in incidence of tumors in the different species are due chiefly to the fact that dogs, cats, and horses usually live out their normal life spans, and cattle, pigs, and sheep are killed for meat when young. That cancer of the mammary gland of the cow is extraordinarily rare may have some significance in the human subject. Primary tumors of the respiratory and nervous systems are rare in dogs and cats. Tumors in animals are less malignant and produce fewer metastases than those in man, but animals are customarily destroyed early in the course of cancer. There exists a fertile field for the comparative oncologist.

Cotchin, E.: Some comparative aspects of neoplasia in domesticated mammals. Brit. J. Radiol. 29:311-316, June, 1956.

Anoxia—Cause of Cancer?

The author's theory of the cause of cancer, proposed in 1950, is restated and amplified. Attempt is made to reconcile his idea of anoxia as the cause of cancer with Warburg's work on the excess of lactic acid in cancer cells. Anoxia goads the cell into cancerous change by diverse actions—carcinogens and their ilk on the one hand and cell factors on the other. Reversion of the cell to a more primitive type of metabolism requiring less oxygen and allowing it to escape from physiological control—this, to the author, is cancer. Chronic lack of oxygen causes cancer. Cells lacking oxygen fall prey to carcinogens at lower thresholds than do normal cells. The author agrees with Warburg that we have all but one or two pieces of the jigsaw puzzle. Prophylaxis is important. Public education should emphasize good hygienic habits—diet, rest, vacations, moderation in smoking and drinking, avoidance of contaminants in air and food, etc. Carcinogenic materials should be more strictly regulated. More harm than good may come from radiation and hormone therapy if we are not vigilant. All anticarcinogenic agents are carcinogenic themselves, and may precipitate more cancer than they cure. Increase in fundal cancer of the uterus is evidence of the harm that may come from promiscuous use of hormones. Every physician should realize the long latent period of cancer, as exemplified by bronchogenic cancer from smoking.

Bicknell, E. A.: Cancer and anoxia; a further evaluation of clinical and experimental trends. J. Michigan M. Soc. 56:456-460, April, 1957.

Origin of Cancer

It is deplorable that modern medicine is interested only in new data and in statistics and not in the philosophy of science. This is exemplified by some of the hypotheses concerning the cause of cancer. Warburg's view (Abstr. in *CA—Bull. Cancer Progr. 6*:146, 1956) that cancer cells originate through injury to respiration followed by increased fermentation is contradicted by the following facts: (1) Impaired respiration plus increased fermentation is not characteristic of cancer. (2) The following characteristics of cancer are not explained by Warburg's view: (a) Cancer develops from a single cell, and oxygen lack cannot affect one or even only a few cells. (b) Cancer develops not at the site of greater injury, but at a distance where the damage is less, as following benzpyrene injection. (c) The identifying properties of the cancer cell such as hyperchromatosis, increase in size of the nuclei, etc. (d) Invasiveness. (e) Contact spread. (f) Production of cancer by heat, ultraviolet radiation, hormones, and repeated proliferative inflammations. (3) Irritants increase blood supply and therefore oxygen supply. Lack of oxygen has never been shown to lead to cancer in vivo. Small doses of narcotics, such as ethylene, chloroform, and ether, stimulate rather than depress respiration. (4) Intensive glycolysis cannot be an energy substitute for respiration in cancer cells. (5) Warburg's statement, that the continual discovery of carcinogenic agents may hinder preventive measures and thereby become responsible for cancer cases, is incomprehensible. (6) Reversibility of injuries to respiration has been evidenced by regression of the tumor. (7) No event can be called a cause of a process unless it is regularly followed by that process. (8) The author published a physico-chemical explanation of the origin of cancer cells in 1929 and 1944. Its premise was that living cells contain a surplus of oxygen. The existence of oxygen in colloidal dispersion in addition to its presence in molecular dispersion can explain not only impairment of respiration and its increase during work and the growth of cells but also all known characteristics of cancer and the stimulating effect of small doses of narcotics. Not lack of oxygen but deficient oxygen activation is an essential part of the mechanism of conversion of an aerobic into an anaerobic cell.

Roder, F.: Discussion: an analysis of Warburg's view on the origin of cancer cells. Philos. Sci. 23:343-347, Oct., 1956.

at a glance . . .

one-minute abstracts of the current literature on cancer of the skin . . .

Keratoacanthoma of Lip

Molluscum sebaceum or keratoacanthoma is a benign, self-healing skin tumor which grows rapidly for six or more weeks, reaches a maximum diameter of 1 to 3 cm., and then slowly regresses, leaving a flat, atrophic area with a crinkly, hypertrophic edge. While it is growing this tumor resembles squamous carcinoma so closely both clinically and histologically that many of these lesions have been so diagnosed and treated. Keratoacanthoma occurs about half as frequently as squamous carcinoma. A more general awareness of its incidence will disclose many such tumors on the lip, perhaps as many as on the rest of the skin. Outdoor workers with light complexions and fair hair are especially subject as such skins are readily irritated by strong sun and harsh weather, and, after years of exposure, commonly show keratoses on the face and backs of the hands. A case is described in a sandy-haired, ruddy farmer, aged 48. The lesion appeared on the site of a "cold sore." There was no lymph-node enlargement and the only treatment was the local application of hydrocortisone ointment and antibiotics. Biopsy at six weeks showed an appearance consistent with the diagnosis of keratoacanthoma. The possibility of squamous-cell carcinoma could not be excluded until one year later when the lip was entirely normal, confirming the diagnosis of keratoacanthoma.

Whittle, C. H., and Davis, R. A.: Kerato-acanthoma of lower-lip red margin. Lancet 1:1019-1020, May 18, 1957.

Malignant Tumors of Skin

Malignant neoplasms of the skin include, in addition to the primary lesions, metastases from internal malignant disease and those malignant conditions developing in certain diseases of the skin. Metastases reach the skin by direct spread from underlying tumors, direct spread through lymphatics, dissemination through lymphatics, and by dissemination through the blood stream. The breast is the site of origin of 50 per cent of cutaneous metastases, the stomach 15 to 31 per cent, the lung 12 per cent, the uterus 9 per cent, and the kidney 9 per cent. Some tumors have predilection for the scalp, namely, 33 per cent of carcinomas of the breast and 20 per cent of others. Cutaneous metastases are generally indicative of progression and early fatal termination. The commonest type of metastatic cancer from the breast is inflammatory carcinoma. From 25 to 35 per cent of cases of Hodgkin's disease have cutaneous manifestations and in about 10 per cent these were the initial symptom. Cutaneous diseases reported to be followed by malignant

change include psoriasis, eczema, lichen planus, scars from burns, trauma, syphilis, tuberculosis, lupus vulgaris, lupus erythematosus, cheilitis glandularis, pruritus ani after tar application, radiodermatitis, arsenical dermatitis, rhinophyma, and herpes zoster.

Beerman, H.: Some aspects of cutaneous malignancy. Am. J. M. Sc. 233:456-472, April, 1957.

Treatment of Multiple Basal-Cell Epithelioma

Multiple, superficial, benign basal-cell epitheliomas are usually treated by electrodesiccation. Other methods include surgical excision, thorium X, solid carbon dioxide, podophyllin in compound benzoin tincture, and liquid oxygen. Liquid nitrogen with a temperature of –195.8° C is preferred to solid carbon dioxide with temperature of –57° C because of its lower temperature and ease of application, and to liquid oxygen with a temperature of –185° C because of freedom from danger of explosion. Liquid nitrogen was applied in treatment of seven patients having from one to one hundred or more lesions. The liquid was applied with a cotton applicator with moderate pressure to each area for about ten seconds. The method is a simple, quick, inexpensive office procedure with a minimum of risk. There is little pain and no general reaction. Usually ten to fifteen minutes after treatment there is mild to moderate pain. Twenty-four hours later vesiculation or crusting is present. Healing is complete in ten to fourteen days. Scarring is minimal and the final result is superior to that obtained by scalpel surgery, electrosurgery, or roentgen therapy. This method is proposed as an excellent treatment for this condition.

Ickel, L. G.: Multiple superficial benign basal-cell epithelioma. A.M.A. Arch. Dermat. 76:105-106, July, 1957.

Skin Biopsy

Discussion of biopsy technique for tissues other than skin is usually limited to the instruments used and the technical procedure. These secondary technical considerations are less important in performing biopsy of the skin than are the selection of proper site for the biopsy, the removal of an adequate specimen, and the use of proper fixative and appropriate stains. Many pathologists prefer to examine specimens that are removed entirely within the lesion so that only pathological tissue is submitted. However, much can be gained by removing the biopsy specimen from the border of the lesion so as to include a small area of normal tissue. The skin at the selected site is cleansed with soap and water and sterilized by application of alcohol or zephiran solution. Local anesthesia is produced by injection of 2 per cent procaine hydrochloride. The preferable method for obtaining a suitable specimen is cold-steel surgical removal. The specimen should be plainly marked with a line of transection to avoid the pathologist's seeing only normal tissue. For routine sections 10 per cent formalin is used as fixative. The solution should be buffered to pH levels above 6, with calcium or magnesium carbonate, to avoid formation of granules of formaldehyde pigment which may be confused with skin-pigment granules. Specimens fixed in this manner are suitable for frozen sections to be examined for fat as well as for further processing through paraffin. A gross description of the lesion should be submitted together with the specimen.

Caro, M. R.: Skin biopsy technique. A.M.A. Arch. Dermat. 76:9-12, July, 1957.

Occupational Skin Cancer

Cancers of the skin may be caused by mechanical, thermal, chemical, or radiation stimulation. Industrial cancers are classified as accidental and occupational. A skin cancer of the former group is caused by the sudden and violent action of an external force, a single traumatism whose date of origin is definitely fixed. These are the accidents of employment. The latter result from local, chronic irritation from repeated lesser mechanical, thermal, chemical, or radiation traumatisms. They are in the group of industrial diseases that are compensable and

against which employers take preventive measures. In traumatic skin cancer the delay between the time of the traumatism and the diagnosis of cancer varies widely. After a period of years a more recent carcinogenic etiologic factor should be sought. Among the precancerous danger signals of skin cancer are erythema, eczematous or allergic dermatitis, pigmentation, atrophic plaques, telangiectasis, folliculitis (especially in oil handlers), hyperkeratoses, lichenification, and sebaceous cysts. Arsenic compounds are notorious for their causing cancer of the skin; cobalt from the Canadian mines, and cement, perhaps from contained chromium, have been incriminated. Luminous radiation, ultraviolet, roentgen rays, radium, and radioactive substances cause skin cancers that develop very slowly, generally in a minimal period of five to ten years. The danger of skin cancer is being constantly increased by the modern extension of the manufacture and industrial uses of substances known, and not yet known, to be carcinogenic.

Touraine, A.: Les cancers cutanés du travail. [Occupational skin cancers.] Arch. mal. profess. 16: 563-79, 1955. [Bull. Soc. franç. dermat. et syph. 563-79, No. 2 bis, 1955.]

Environmental Skin Cancer

Among the occupational carcinogens causing skin cancer are coal tar, pitch, asphalt, tar oil, synthetic hydrogenated coal oil and tar, shale oil and paraffin oil, petroleum fuel oil, diesel oil, lubricating oil and grease, cutting oil, arsenic, ultraviolet radiation, roentgen radiation, and radioactive isotopes. Local public health agencies and the medical profession should assume an important role in the discovery and preventive control of environmental cancer hazards. Adequate familiarity with the various recognized, suspected, and potential environmental carcinogens is a fundamental requirement for such control. Such knowledge should include information concerning specific occupational activities, industries, industrial goods, industrial wastes in the form of air, water, and soil pollutants, and environmental poisons. These may be pesticides, herbicides and household and sanitary goods, additives and contaminants of foodstuffs, and medicinal agents. The latent period of occupational cancers may be fifty years or more. Modern industrialization has increased the potential hazards from carcinogens as the result of occupational activities, use of industry-related consumer goods, synthetic medical chemicals, production of apparatus for ionizing radiation, and pollution of the air, water and soil with industrial wastes.

Hueper, W. C.: Environmental cancer hazards: A problem of community health. South. M. J. 50:923-933, July, 1957.

Skin Cancer Latent a Half Century

In 1898 a woman 21 years of age was given a diagnostic roentgen examination for renal calculi. It is probable that the kilovoltage used was about 100 kvp at a skin-target distance of about 20 cm. The exposure over the right upper abdomen was said to have lasted about an hour. The skin dose, including back-scatter probably did not exceed 2000 r. In two weeks a blistering skin reaction appeared but subsequently healed. In 1947 an ulcer appeared, 7.5 x 5 x 1 cm., with raised edges and surrounded by an atrophic skin area 13 x 12 cm. which contained areas of pigmentation and numerous telangiectases. Biopsy showed extensive squamous-cell carcinoma. Surgery was not possible on account of the poor general condition of the patient. An attempt at radiotherapy showed the lesion to be as radiosensitive as similar squamous-cell carcinomas. A total dose of approximately 3000 r on the skin over thirty-nine days was used. The lesion failed to heal and the patient died two years later at the age of 72.

Mitchell, J. S., and Haybittle, J. L.: Carcinoma of the skin appearing 49 years after a single diagnostic roentgen exposure; report of a case. Acta radiol. 44:345-350, Oct., 1955.

Radiation-Induced Cancer

A female patient, aged 70 years, under the care of Professor D. W. Smithers, was treated by radiotherapy in 1898, three years after Roentgen's discovery. The

treatment for hairs on the face was given daily for several months. Subsequently the patient developed ulceration on the chest, neck, chin, and face. Fifty-six years after first exposure to roentgen rays there were marked radiation changes and a necrotic ulceration on the front of the chest. Histologic study showed squamous-cell carcinoma with metastases to the lungs and axillary lymph nodes.

Cade, Sir S.: Radiation induced cancer in man. Brit. J. Radiol. 30:393-402, Aug., 1957.

Prednisone in Radiation Dermatitis

In sixteen patients with basal- and squamous-cell epitheliomas treated with prednisone, 10 to 20 mg. daily, radiation dermatitis and scarring were minimized. This therapy did not interfere with tumor response to radiation. When the drug was given before redness appeared and continued in adequate dosage during the course of irradiation, the period of inflammation was shorter than when therapy was withheld until erythema appeared. Only two cases showed vesiculation. Although this therapy lessens radiation damage it apparently does not interfere with its antitumor action.

Mathewson, J. B.: Postradiation inflammation reduced by prednisone. New York State J. Med. 56: 3903-3906, Dec. 15, 1956.

Sweat-Gland Carcinoma

Twenty-two previous cases and one of the authors of metastasizing sweat-gland carcinoma are reviewed. Regional lymph-node metastases were the first manifestations of the spread of the tumor in eighteen of the twenty-three cases. In twelve cases the metastatic lesion was limited to the regional lymph nodes; in eleven dissemination of metastases occurred and caused death. In the cases brought to necropsy metastases occurred in lungs, pleura, liver, adrenals, ribs, pelvis, vertebrae, subcutaneous tissue, thoracic and abdominal lymph nodes, as well as in the regional lymph nodes. The authors' case was one of sweat-gland tumor of the plantar surface of the left foot of eighteen years' duration. A metastatic lesion to an inguinal lymph node occurred ten months after excision of the primary tumor.

Teloh, H. A.: Balkin, R. B., and Grier, J. P.: Metastasizing sweat-gland carcinoma. A.M.A. Arch. Dermat. 76:80-86, July, 1957.

Skin Cancer Forty Years after Fluoroscopy

In 1912 a 42-year-old patient was given a single fluoroscopic examination following an accident. The next day a skin reaction developed on the anterior chest wall, which soon ulcerated. Despite various therapeutic procedures the ulceration remained unhealed for forty years and in 1952 a tumor developed on the margin of the ulcer. Biopsy showed anaplastic epidermoid carcinoma on the basis of a long-standing radiation ulcer. The chronic inflammatory irritation was considered to be a predisposing factor.

Rübe, W.: Durch einmalige Röntgendurchleuchtung verursachtes Ulkuskarzinom mit 40jähriger Latenzzeit. [Ulcer carcinoma following single fluoroscopic examination performed forty years earlier.] Strahlentherapie 94:239-244, 1954.

Visible Tumors

All physicians in the course of their daily practice see benign, visible tumors, think nothing of them, and do not mention them to the patient. The benign lesions of immediate concern are the so-called moles or pigmented nevi. It is true that malignant melanoma may arise from the junctional nevus but the majority of the melanomas apparently originate from previously uninvolved skin. Removal of all nevi is highly impractical but those of the junctional type should be removed from palms, soles, fingers, toes, the anogenital region, and sites where they are subject to repeated trauma or irritation. In addition, nevi that bleed, show change in pigmentation, irregular progression or growth at the border and summit, or have a halo of pigmentation should be excised and examined microscopically. The predominant precancerous lesions of the skin are the senile actinic keratoses arising in weather-beaten and chataigne skin, arsenical kera-

toses, and keratoses arising in lesions of radiodermatitis. These lesions are classed as precancerous because squamous-cell epithelioma develops in approximately 20 per cent and because they are regarded by some pathologists as epithelioma (carcinoma) in situ. Arising from apparently normal skin or from the precancerous lesion, squamous-cell epitheliomas are characterized by a heavy, indurated border with an inflammatory halo and central crusting or ulceration. Occasionally the entire lesion may be granulomatous or verrucous. Although it does not metastasize, the basal-cell epithelioma is malignant because of its invasive character. It is the most frequently encountered cancer of the skin, manifesting classically a solitary, pale, translucent nodule. As it enlarges, a pearly, wide or narrow border with a central depression, which may ulcerate, develops. Malignant melanoma usually metastasizes early and rapidly, exhibiting irregular pigmentation in shades of blue and black, although it may have no pigmentation (amelanotic melanoma). Another group of visible malignant tumors are those produced by the lymphomas, i.e., Hodgkin's disease, lymphosarcoma, mycosis fungoides, and the leukemias. These tumors although usually specific microscopically, may be associated with many nonspecific toxic eruptions varying from simple erythema, urticaria and bullous states to universal erythroderma. Generalized pruritus with or without an eruption is not infrequent. Finally, malignant lesions of deep organs may metastasize to the skin, frequently beginning in the scalp, and become visible. Biopsy including the microscopic interpretation of such a lesion will provide the diagnosis and save the patient numerous surgical procedures.

Kierland, R. R.: Visible tumors. Geriatrics 12:162-163, March, 1957.

Sunbathing and Cancer

The exact points at which the cumulative effects of the sun manifest themselves in irreversible skin changes are individually very different. The connective tissue of the skin undergoes degenerative changes that are reflected on the surface by wrinkles and a coarsening of skin texture. The lips sometimes become scaly, fissured, thickened, and eroded. Abnormalities of keratinization of different types and degrees develop. Some of these changes are premalignant keratoses, the end result of which can be skin cancer. The safest and simplest method of acquiring an attractive tan is gradual exposure to the sun. No suntan preparation should be used in this method of tanning by gradual exposure. A suntan preparation that permits users to tan must allow some burning rays to pass to the skin. Suntan preparations should always be used by patients with solar herpes, lupus erythematosus, polymorphous light eruptions, keratoses, skin cancer, and those previously treated with roentgen ray.

Ways and Means to Safe Sunbathing. [Report of the Committee on Cosmetics.] J.A.M.A. 161:1480-1483, August 11, 1956.

"Self Healing Carcinoma"

Only within the last two years has keratoacanthoma been differentiated from squamous- and basal-cell carcinomas. Until very recently this benign skin lesion was diagnosed and treated as a malignant neoplasm. Only last year such a tumor was diagnosed in a pathology laboratory of a U. S. Public Health Service hospital and at the Armed Forces Institute of Pathology as a squamous carcinoma. Review of the histologic preparation placed it definitely as a keratoacanthoma. This benign lesion must also be differentiated from senile keratoses, common warts, molluscum contagiosum, and blastomycosis. Surgical excision is probably the treatment of choice, followed by biopsy. The lesions may disappear spontaneously. There are probably two etiologically distinct types of keratoacanthoma: the single type related to aging and exposure to sunlight and the multiple type linked with exposure to petroleum products and tars.

Monroe, W. M.: Keratoacanthoma: A frequent but rarely recognized skin lesion confused with squamous carcinoma. South. M. J. 50:852-854, July, 1957.

Skin Cancer: Its Causes, Prevention, and Treatment

Frederick D. Malkinson, M.D., and Stephen Rothman, M.D.

The accessibility of cutaneous cancers offers two unique opportunities: 1) the laboratory and clinical investigation of factors important to the predisposition and development of malignant cutaneous neoplasms, and 2) the early diagnosis and adequate treatment of these tumors.

Perhaps the earliest contribution to our knowledge of carcinogenesis was Percivall Pott's observation in 1775 that scrotal cancer in chimney sweeps resulted from chronic soot exposure. In the 19th and 20th centuries clinical observations revealed that skin cancers also arise from long-standing contact with tars, pitch, and petroleum products (lubricating oils, etc.). Experimentally, repeated applications of tar and later on of single polycyclic hydrocarbons to the skin of mice and rabbits have reproduced these malignant growths.

Although chemical carcinogenesis was perhaps the first important observation in the pathogenesis of skin cancer, other significant predisposing or "irritant" factors are now recognized.

Clinical studies long ago suggested a relationship between the development of skin cancers and chronic exposure to sunlight. In a review of our own patient material,[3] for example, it was found that 91.1 per cent of all skin cancers occurred on uncovered parts such as the face, ears, neck, and dorsa of hands (Table I). In many individuals exposure to excessive amounts of sunlight over the years results in a severe form of senile atrophy of the skin. The skin becomes thin, sallow, dry, wrinkled, slightly scaling, and inelastic; often freckles, lentigines, and telangiectases are present. Such changes are frequently seen in sailors, farmers, fishermen, habitual sunbathers, etc., and

Table I

Distribution of Skin Cancers According to Site*

Exposed		Partially exposed		Nonexposed	
Site	%	Site	%	Site	%
Face	87.0	Arm	1.2	Back	3.2
Ear	1.6	Scalp	0.9	Chest	1.2
Neck	1.6			Abdomen	1.2
Hand	0.9			Thigh	0.9
	91.1		2.1		6.5

* Based on 246 cases seen in the Dermatology Clinic of the University of Chicago from 1930 to 1946.

Department of Medicine, Section of Dermatology, University of Chicago Clinics: Stephen Rothman, Chairman.

[For references see p. 205]

are more common in blonde or red-headed persons. The frequency of precancerous keratoses and carcinomas in these individuals is exceedingly high. To substantiate further the role of chronic sun exposure Public Health Service statistics[1] have shown that precancerous keratoses occur six times as frequently in the southern section of the United States as in the northern, and that the incidence of skin and lip cancers is about two and one-half times as great in the southern states (at 32° latitude) as in the central states (at 38° latitude). Experimentally, too, it has been demonstrated in mice that chronic exposure to intense ultraviolet light produces both cutaneous keratoses and malignant tumors. It is now established that the carcinogenic rays of sunlight are the same as those responsible for sunburn (2800-3100 Å in the ultraviolet part of the spectrum).

A dramatic association of sunlight exposure with malignant cutaneous tumors is seen in the rare syndrome, xeroderma pigmentosum, where extreme sensitivity to sunlight in infancy or early childhood results in severe atrophy or "farmer's skin" after only a few brief exposures. Individuals with xeroderma pigmentosum seldom survive to adulthood because of the early development of multiple malignant cutaneous neoplasms. Since this disorder is inherited as a recessive trait, it illustrates a link to genetic factors, as well as to sunlight exposure, in the pathogenesis of skin cancers.

Another factor related to the role of sun exposure concerns the low incidence of carcinoma in dark-skinned races. The assumption is that this is the result of resistance to the sunburn-producing rays, and it indicates that racial factors are also of some importance in the predisposition to skin cancer.

In addition to specific chemicals and to part of the ultraviolet-light spectrum, other forms of chronic irritation such as heat, physical trauma, and ionizing radiation may be followed by malignant change in the skin. Almost eighty years ago Kangri cancers were first described in Kashmir as arising on the thighs or abdomen at the point of contact with the Kangri jar, a brazier of hot coals carried under the clothing for warmth in cold weather. The frequent occurrence of leukoplakia and oral cancer in tea-tasters after repeated exposures to very hot tea has also long been recognized. Mechanical trauma has preceded skin cancers in such well-known cases as the "collar-button" lesions seen in males during the stiff-collar era. Another example still encountered at the present time is the occasional occurrence of carcinoma under the nose-piece of eyeglasses.

Chronic radiodermatitis occurs as a late change following several relatively small exposures or after acute radiodermatitis resulting from one or more massive exposures. The dosage levels of roentgen ray tolerated by the skin are well established but after excessive exposures from accidents and other causes the skin ultimately shows chronic changes of dryness, atrophy, hyper- and hypopigmentation, and telangiectases. Keratoses which may become malignant, basal-cell carcinomas, and squamous-cell carcinomas, as well as other tumors, not infrequently develop in such altered skin.

So far the observations recorded have indicated that the most significant factor in the pathogenesis of skin cancer is that of exposure to chronic chemical, actinic, thermal, or mechanical injury. Some importance may also be attributed to racial and genetic factors. In the consideration of chronic injury as the foremost etiologic agent it seems almost certain that all of the diverse forms of trauma mentioned produce analogous physiological and pathological disturbances in the skin. Normally skin keratin is continuously desquamated as ultramicroscopic particles, but after repeated ultraviolet-light irradiation or simple mechanical rubbing the keratin layer becomes greatly thickened as a result of inhibition of physiologic peeling. This "superkeratinization" with formation of a harder, thicker keratin represents the initial biologic alterations in epidermal cells resulting from repeated minor traumata. It is the first step in malignant degeneration and is followed later by cellular anaplasia and invasion of the under-

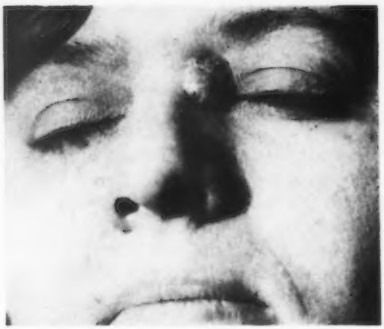


Fig. 1. Basal-cell carcinoma, left inner canthus.

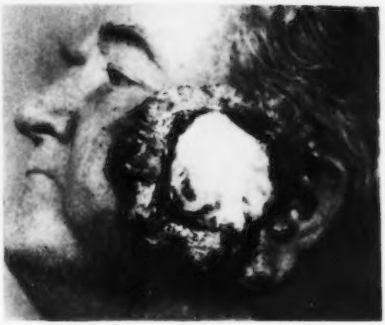


Fig. 2. Mixed-cell carcinoma, successfully treated with roentgen rays.

lying dermis. Undoubtedly, at least in the development of the two most common precanceroses of the skin and mucous membranes—senile keratosis and leukoplakia—chronic trauma and superkeratinization are the principal factors.

Senile keratoses are seen in older, and occasionally younger, individuals, occurring on light-exposed areas principally in those who have been exposed to sunlight and the elements for many years. The lesions may be single or multiple and usually accompany changes of senile atrophy in the skin. Senile keratoses vary in size from a few millimeters to a centimeter or more, range from red to brown in color, and present a dry, gray-white, adherent scale which is the only palpable element of the uncomplicated lesion. In themselves they are benign and may persist unchanged for many years. Eventually, however, carcinoma, usually of the squamous-cell type, develops in about 20 per cent of untreated lesions.

Leukoplakia may be regarded as the counterpart of senile keratosis as it occurs on the mucous membranes. The lips and the mouth—particularly the buccal mucosa and the anterior dorsal surface of the tongue—are the sites most frequently involved, but vulvar leukoplakia is not uncommon after the menopause. The condition is characterized by opalescent spots which later become milky white. These lesions are sharply circumscribed and in time the surface becomes rough, thickened, verrucous, and fissured. Subjective symptoms are nil unless fissures are present or secondary infection occurs. The early, flat, opalescent lesions are almost invariably benign, but when the patches become hyperkeratotic and fissured, malignant degeneration may be found. As with keratoses, leukoplakia may remain benign and show little change for many years, but ultimately squamous-cell carcinoma develops in 20 to 30 per cent of untreated patients.

The principal etiological factor in the development of leukoplakia is chronic local irritation. Mechanical irritation may result from ill-fitting dentures, faulty occlusion, carious teeth, improperly constructed crowns and bridges, and habitual chewing (inner surface of lip or buccal mucosa). Leukoplakia is not uncommon in smokers and may result from chronic exposure to heat (as on the lip at the contact spot of a pipe stem) or, perhaps, from the chemical carcinogenic action of tobacco. Chronic exposure to sunlight is also an important factor in leukoplakia of the lips and in its predilection for the lower lip. Leukoplakia has often been observed in syphilitics, too, although the reason for the association of the two conditions remains unknown. Leukoplakia is more common in men than in women by a ratio of almost 10 to 1, and like senile keratoses, is found most frequently

in middle-aged and older individuals.

Skin cancers arise predominantly on exposed areas from precancerous conditions or from normal skin. There are two principal types of carcinoma and these are classified definitively on the basis of histopathological changes: basal-cell carcinoma, showing proliferation, anaplasia, and invasion of the underlying dermis by cells of the basal-layer type, and squamous-cell carcinoma, in which tumor growth derives from similar changes in the cells of the malpighian or prickle-cell layer of the epidermis. Occasionally two variants of the microscopic features of these fundamental forms of carcinoma are found: either the tumor cells present are a type intermediate between basal and squamous cells, or the two cell types maintain their identity but are found together in the same tumor (mixed-cell tumor).

Skin cancers occur principally in middle-aged and older individuals; less than 2 per cent occur in patients less than thirty years of age. Men outnumber women 2 to 1. Carcinomas are usually single but are multiple in up to 20 per cent of cases, and both types of carcinoma may be found in the same patient. A survey taken in 1952 showed that skin carcinomas accounted for only 2.2 per cent of all cancer fatalities in the United States.[4]

Basal-Cell Carcinoma

Approximately 65 per cent of all malignant skin tumors are of the basal-cell type. These lesions are characteristically slow growing and respond most satisfactorily to adequate therapy if the tumor is not far advanced. Metastases are almost never seen, occurring only rarely after extension to underlying bone. The course of the untreated lesion, however, is one of slow but persistent local peripheral and invasive growth. In the late stages with deep invasion of bone, and particularly with involvement of structures such as the orbit or the cranial cavity, it may be impossible to save the patient.

Basal-cell carcinomas vary considerably in their clinical appearance. Often the lesion first appears as a firm, waxy papule or nodule with telangiectasia. Following enlargement of the tumor the center usually becomes depressed leaving a pearly border. Erosion with crusting and bleeding may occur and eventually, as tumor cells invade more deeply, a frank central ulceration with a rolled, raised border is seen (rodent ulcer). Occasionally central healing with atrophic scar formation occurs as the tumor spreads peripherally in a rather superficial manner. Globular forms of basal-cell carcinoma are also not uncommon. Infrequently increased amounts of melanin pigment occur in these tumors leading to some difficulty in differential diagnosis from melanoma. An uncommon but distinctive clinical variant is the morphea-like basal-cell carcinoma. This is a flat, yellow to white, indurated, and rarely ulcerated lesion characterized by considerable fibrosis following a determined but unsuccessful attempt by the tissues to eradicate tumor cells.

A more benign form of basal-cell tumor is the superficial erythematous basal-cell carcinoma. This lesion usually occurs in multiple numbers rather than singly and in contrast to the other clinical types has a predilection for the covered areas of the body. Superficial basal-cell carcinomas appear as flat, red, slightly scaling patches which sometimes enlarge to several centimeters in diameter and often show a fine threadlike, raised border. Other characteristics may include traumatic bleeding, crust formation, erosion or ulceration, and central scarring. Although histologically these lesions show buds of proliferating basal cells still attached to the overlying epidermis, invasion of the dermis and underlying structures by detached tumor cells may occasionally occur, as it does in other varieties of basal-cell carcinoma.

Squamous-Cell Carcinoma

Squamous-cell carcinoma of the skin is a common entity, although it is seen less frequently than basal-cell carcinoma. It is by far the more dangerous of the two lesions, however, since it is faster growing and may metastasize to regional lymph

nodes and beyond to other tissues and organs. The tumors may be slow growing and remain localized for many years, but often they grow swiftly either from the onset or after periods of quiescence. In 95 per cent of cases they are found on the head or dorsa of the hands, arising from normal skin or precancerous lesions such as senile keratosis or leukoplakia. Squamous-cell carcinoma also occurs occasionally in areas of radiodermatitis, at the edge of long-standing ulcerations, or in old scars due to thermal or chemical injury.

The clinical appearance of this tumor varies considerably. Often it appears as a crusted ulcer surrounded by a firm, wide, indurated border with undermined edges. Some lesions present as flat, raised, infiltrated papules or nodules without a central depression. Occasionally verrucous and vegetative lesions are seen. Although frequently it is possible to distinguish basal-cell carcinomas from squamous-cell lesions clinically, often the most experienced observers may err. Biopsy should always be performed to substantiate the suspicion of carcinoma and to establish the specific type.

Prevention and Treatment

It is obvious that prevention of cancer means essentially removal of those factors producing chronic skin or mucous membrane irritation. It may be advisable, for example, to acquaint young individuals, who have outdoor occupations but as yet show little skin change, with the consequences of long-term sunlight exposure. Where feasible, the older patient with "farmer's skin" should be persuaded to change his outdoor occupation and to avoid sunlight. An effective sunscreen preparation such as a 15 per cent para-aminobenzoic acid ointment can be prescribed for times when sun exposure is unavoidable. In patients with leukoplakia appropriate dental restorations or cessation of smoking may suffice to induce remission. Those exposed to occupational carcinogens (tar, pitch, petroleum derivatives) may be forced at length to change their jobs, although industrial control methods in this country at the present time are excellent. In addition, the physician must realize that prolonged regular observation is most important for those patients subject to occupational cancer, for persons with persistent or recurrent leukoplakia, and for those with multiple, senile keratoses. Any lesions showing suspicious changes (redness and induration at the base of a keratosis, sudden thickening of a patch of leukoplakia) should be examined by biopsy as should all new lesions suspected of being malignant. Persons working with radioactive materials or roentgen rays should also have periodical medical examinations.

Measures suitable for the treatment of senile keratoses depend on the history and appearance of specific lesions. The small keratosis which has shown no growth or surface change may be left untreated provided the patient returns regularly for observation. Often a keratolytic ointment, such as 2 per cent salicylic acid in unguentum aqua rosae applied two or three times daily, keeps the keratinization satisfactorily controlled. When a keratosis persists and particularly when it enlarges, becomes widely erythematous, or begins to show infiltrative changes, biopsy followed by electrocoagulation and curettage is indicated. If malignant change has occurred further treatment is carried out as described.

Biopsy is advisable for all patients with leukoplakia. If the patches are flat and opalescent, correction of local irritant factors and continued observation suffice. Persistent leukoplakia or lesions which become rough and thickened should be biopsied at sites which appear to be most advanced and then treated by thorough electrodesiccation. For larger lesions surgical removal is also satisfactory. Where squamous-cell carcinoma is found histologically, surgery or radiation therapy with removal of possibly involved lymph nodes is indicated. For persistent widespread leukoplakia of the lip, with or without carcinoma, a satisfactory surgical procedure is a wedge or horizontal resection with extension of the mucous mem-

brane of the inner lip to produce a new vermilion border.

There are two main forms of therapy for previously untreated skin carcinoma: irradiation (roentgen rays or radium) and surgical removal.

Radical surgical excision is chosen by many, and according to some statistics its results are satisfactory. However, radical surgery is difficult or has disfiguring effects in many sites about the face such as eye canthi, ala nasi, etc. Furthermore, one of us (S.R.) has observed relatively frequent relapses after surgery even when wide excision was carried out.

Electrocoagulation with curettage is unreliable and is best restricted to the treatment of recurrent carcinomas at sites where further roentgen-ray therapy or surgery is not practical. The local use of caustics is to be condemned except, in expert hands, for the rarely indicated special technique developed by Mohs.[2]

Our own preference is for roentgen-ray therapy. With competent techniques this treatment is without significant trauma or discomfort to the patient and is the only satisfactory method for lesions which are difficult to remove surgically. Cosmetic results, too, are usually quite satisfactory. Cure rates in excess of 95 per cent for basal-cell carcinomas are obtainable with irradiation. When roentgen-ray therapy is used a margin of at least 4 to 6 mm. of seemingly uninvolved skin should be included about the circumference of the irradiated area. Fractional dosages are routinely used, the amount of radiation given at each treatment depending on the size and location of the tumor. Since 1947 our method of treatment has been to give 5400 r in equal fractional doses administered three times weekly until a total of nine treatments has been given (i.e., 9 x 600 r). Small lesions over ample subcutaneous tissue are sometimes treated in five sessions. For lesions on thin skin (such as the ear) and for those over 2 cm. in diameter 15 x 360 r are given. The factors for the radiation administered are TSD 20 cm., 80 kv, 10 ma (inherent filtration 0.71 mm Al).

The case records of sixty-eight patients with all types of skin carcinomas treated with roentgen rays or radium at the University of Chicago Clinics from 1945 to 1950 have been reviewed. To these were added the case histories of six patients treated between 1938 and 1945. In all, seventy-eight carcinomas were treated in this group of seventy-four patients. There were thirty-six basal-cell carcinomas, eleven squamous-cell carcinomas, eight intermediate-cell carcinomas, five mixed-cell carcinomas, eleven squamous-cell carcinomas in situ, and seven superficial, erythematous, basal-cell carcinomas. In all patients the diagnosis was confirmed or established by biopsy and all cases were followed for at least five years. Seventy-one of these tumors were treated successfully without recurrence, although many received therapeutic dosages now recognized as frequently inadequate. Of the seven recurrences noted (all basal-cell carcinomas) six occurred in patients receiving insufficient treatment (1800-3600, r). One recurrence was seen in a patient who had received 4500 r (radium). Of forty-six patients treated with the modern dosage schedule of 5400 r or an approximately equivalent dose of radium, this last individual was the only one to show recurrent tumor growth.

In general, roentgen-ray or radium therapy is effective in the treatment of squamous-cell carcinomas. In large, rapidly growing tumors, however, and for those complicated by regional lymph-node metastases radical surgical removal remains the treatment of choice.

Superficial, erythematous, basal-cell carcinomas present slightly different treatment problems. Because the lesions are superficial electrodesiccation with curettage is a suitable form of therapy and even larger lesions can be treated in stages by this method. Surgical removal can also be recommended for these carcinomas. Although "standard" dermatologic roentgen-ray therapy is successful considerable radiation penetrates to normal tissue below the tumor. Good treatment results, however, may be obtained with very soft (Grenz) rays largely absorbed by the epidermis and the attached tumor cells.

Occupational Cancer of the Skin

Frank C. Combes, M.D.

The cause of cancer including cutaneous cancer is unknown. Although the exciting pathogen may be a virus with an acid-fast, rod-like phase, as described by several investigators, conclusive proof is wanting. One factor in favor of the infectious nature of malignancy is the multiplicity and variability of predisposing causes. Too little attention has been paid the many environmental noxae which are undeniably contributory. While one may postulate specific carcinogens one must admit that cancer results from exposure to many nonspecific environmental agents. These agents certainly warrant our attention.

This approach to the problem is by no means unique. Even with infectious disease control, extensive and laborious epidemiological studies were conducted for many years before we were aware of the true nature and microbial pathogenesis of infectious disease. A century ago when Pasteur and Koch established the microbial origin of infectious disease, the responsibility of extrinsic factors in the cause of cancer was already established. At this early date tar, carbon soot, and petroleum products were mentioned as carcinogens.

Occupational cutaneous cancer has been repeatedly reported in this country for over a half century and attributed to solar radiation, roentgen rays, radium, tar, pitch, petroleum oils, carbon soot, and arsenicals.

It was in 1910 that the first cases of cutaneous cancer attributed to roentgen rays were reported,[2] and similar lesions were described due to coal tar;[13] but not until 1933 were the first two cases, possibly due to industrial contact with arsenic, reported.[16]

Schamberg, in 1910, made the first exhaustive study of the relationship of occupation to cancer of the skin. He emphasized the tars as environmental factors responsible for keratoses and similar premalignant lesions, hesitating to attribute the actual malignancy to contactants. In addition to reporting several cases of his own he collected all previously reported cases.

As long ago as 1906 Hyde commented on the frequency of cutaneous cancer among outdoor workers in the dry and sunny regions of the Midwest. With the exception of skin cancers of suspected solar origin, which many investigators consider to be the most prevalent type, an astonishingly small number of occupational cancers of the skin are reported in the United States. Up to 1950 only seventy-one tar and pitch cancers, sixty-two grease and oil cancers, forty-five roentgen cancers, and eighteen arsenic cancers were recorded. These statistics mean little as in only five states is cancer of any type a reportable disease by legislative action, in Idaho, Nevada, New York, Rhode Island, and Wisconsin. Cutaneous cancer is probably never reported.

Occupational cancers of the skin have certain general features. First, they appear on those areas exposed to the carcinogen (except lymphomas and some of those due to arsenic); they are usually multiple and recurrent, and usually preceded by a nonmalignant precancerous lesion (Table I). Repeated and long exposure to the carcinogen is usually necessary, and these lesions rarely metastasize.

Since involvement of the skin is a prominent feature in leukemia the dermatologist is naturally interested in this phase of malignancy. Benzol leukemia with leukemids is not uncommon in painters, and in workers in can, shoe, and leather factories, rotogravure printing plants, and factories handling radioactive material.

From the New York University Post-Graduate Medical School, New York, New York.

Table I

PRECANCEROUS OCCUPATIONAL LESIONS

LESION	ETIOLOGICAL AGENT
Alopecia areata	Arsenic, radioactive substances, roentgen rays
Atrophy	Pitch, tar, asphalt, radioactive substances, radiation (including ultraviolet)
Eczema	Arsenic, asphalt, pitch, soot, tar
Keratosis Hyperkeratosis Verrucae Ulceration Leukoderma Leukomelanoderma Melanoderma	Anthracene, arsenic, asphalt, creosote, crude mineral oil, paraffin, pitch, sodium nitrate, soot, tar, radioactive substances, radiation (including ultraviolet)
Scleroderma	Crude mineral oils, paraffin oil, radioactive substances, radiation

Mechanism of Carcinogenesis

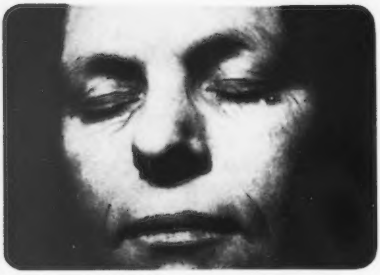
The known or suspected extrinsic or environmental carcinogens act on man in one or more of three different ways. Some carcinogens directly cause cancer; among these are the aromatic amines, the anthracene fractions of tar, and their derivatives.

Other agents coming into contact with the skin cause suppurative or proliferative folliculitides. Among these are the vegetable tar oils, mineral oils, and chlorphenyl compounds. Still others, on coming into contact with tissues, seem to elicit cancers by producing endogenous carcinogenic substances within the exposed tissues. These comprise all the physical rays, heat, light, electromagnetic oscillations, certain metals and metallic compounds, including arsenicals, chromates, and nickel. The metallic group, with the exception of arsenic, is not important in cutaneous cancer but is in pulmonary cancer.

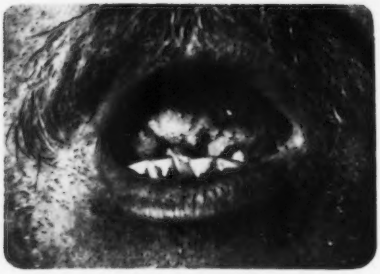
The role played by environmental contributory carcinogens is a subject of wide speculation. Certainly there are qualitative and personal factors involved. Agents such as solar radiation, coal-tar products, and arsenic are universal in distribution but cutaneous cancer is prevalent only in small groups of individuals whose exposure is intense.

Many diverse environmental factors have been indicted in industrial cancer, including diet, medicines, cosmetics, wearing apparel, habits and customs, climate, contaminants in drinking water, air, and foodstuff additives. Certainly there are differences in race, sex, complexion, and type of skin. There is convincing evidence for the environmental cause of cancer. Gover found remarkable variation in different geographical locations. The rates ranged in 1950 from 127 per 100,000 in Rhode Island to 56 per 100,000 in Arkansas. Similar observations were made in Europe where the lowest rates were recorded from the southern countries while the higher ones were usually found in the northern parts of the continent. The highest cancer mortality was observed in Denmark. In 1938 McDowell noted a difference in regional distribution of cutaneous cancer in different points of the United States. He recorded an incidence rate of 157 for Atlanta, 129 for New Orleans, 37 for Detroit, 25 for Pittsburgh, and 24 for Chicago.

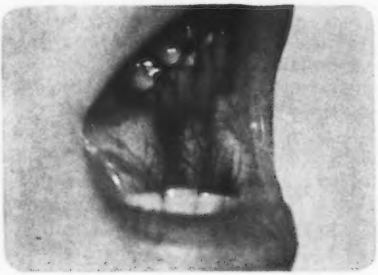
The practical absence of penile cancer in Hebrews, its relative rarity in Moslems, its comparatively high incidence in American Negroes, and its very high incidence in Ceylonese, Javanese, and Chinese certainly do not reflect racial susceptibility but rather differences attributable to hygienic environmental conditions related to incidence of, and age at, circumcision, the



1.

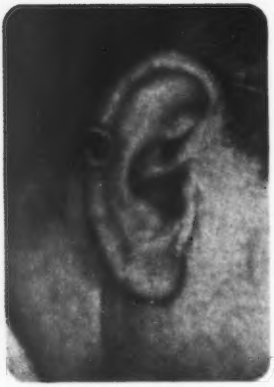


2.

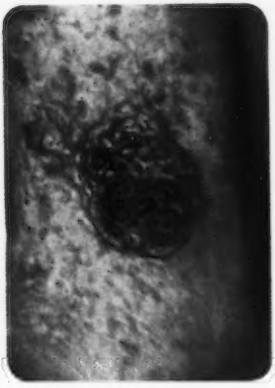


3.

4.

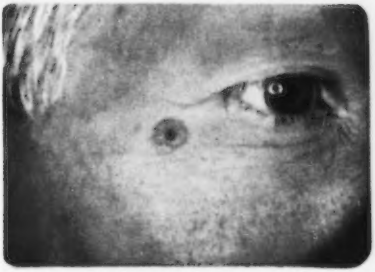


5.

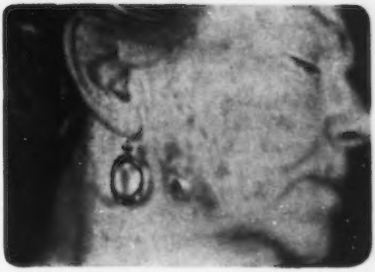


6.

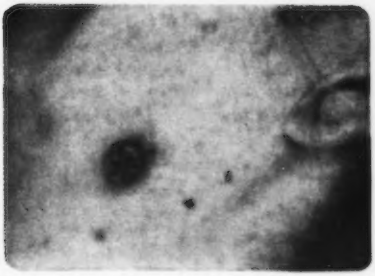
1. Basal-cell carcinoma, lower eyelid.
2. Leukoplakia of the tongue with carcinoma in a luetic.
3. Early leukoplakia, buccal mucosa.
4. Squamous-cell carcinoma, forehead, and multiple, senile keratoses.
5. Squamous-cell carcinoma, ear.
6. Radiodermatitis with squamous-cell carcinoma.



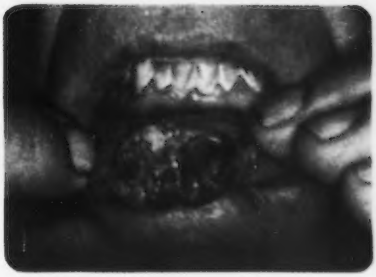
7.



8.

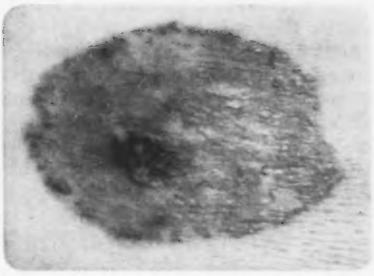


9.



10.

11.



12.

7. Basal-cell carcinoma.
8. Squamous-cell carcinoma over mandibular ramus, and multiple, senile keratoses.
9. Squamous-cell carcinoma.
10. Squamous-cell carcinoma, lower lip.
11. Basal-cell carcinoma, post-auricular.
12. Superficial, erythematous, basal-cell carcinoma, back.

Courtesy of F. D. Malkinson, M.D. and S. Rothman, M.D., Dept of Medicine, Section of Dermatology, University of Chicago Clinics, Chicago, Illinois.

occurrence of phimosis, and similar factors favoring the action of the smegma bacillus.

It is generally recognized that cutaneous pigmentation is protective and responsible for the low incidence of basal-cell epithelioma in those races in which skins are rich in melanin. The lowest incidence of skin cancer is found in the Zulus, the highest in Scandinavians. In the United States an incidence of 18.4 per cent of cutaneous cancer is reported among white cancer patients against 1.7 per cent among colored cancer patients. The native American Indian rarely suffers from cutaneous cancer or lymphomatous diseases.

There is also a sex variation in incidence. The ratio for males to females is four to one.

Statistics also indicate that cancer mortality increases progressively in each lower economic class for all types, except for cancer of the breast. Kennaway established the principle of high cancer mortality in the lower economic classes for scrotal cancer in that he concluded that this type is most prevalent in those men belonging to a class doing the heavier type of labor and usually washing least often. There is no increase in the prevalence of vulval cancer in the lower social classes of women. This sex differential is only coincidental. Classes exposed to sunlight, soot, and grime always show a high incidence. For example in one series recently reported in men employed as stokers and boiler firemen the rate was 225 against 70 in professional men and white-collar workers in the same geographic location. White American soldiers from the Southern states have melanomas less often than those from the Northern states. Occupational factors, therefore, are apparently more important than race, sex, age, and social class.

In determining the responsibility of occupational contactants in causing malignant changes there are many pitfalls which must be avoided. First, it is well known that in most instances contact with the carcinogen must be protracted or repeated over a long period. The actual malignant neoplasm may be preceded by a so-called precancerous lesion which of itself may eventuate in the malignant change many years after the individual has been separated from the suspected carcinogen.

Secondly, there should exist a so-called "lag period." This is an essential feature with some coal-tar fractions, with radioactive substances, and following the ingestion of arsenicals and selenium. By "lag period" is meant a period of apparent latency, after exposure, before visible evidence of malignant disease.

A third pitfall is failure to appreciate the normal incidence of skin cancer.

A fourth error is the idea that there exists correlation between chemical structure and carcinogenicity. And finally the constant hazard which vitiates conclusions drawn from all small animal investigation of disease is the fact that we do not know whether man is more or less susceptible than the laboratory animals to carcinogens. We do know that variations exist in susceptibility of different animals. The rat, rabbit, and dog are much more resistant than the mouse, while in the monkey even the generally recognized carcinogens are incapable of causing tumors. (Table II.)

Table III lists the industrial carcinogens together with their discoverers and the years of discovery. According to our present concept, the environmental contributory carcinogens are as follows:

1. Chemical carcinogens
   - A. Organic chemicals
     Aromatic compounds: tar, pitch, asphalt, soot, shale oil, paraffin, crude oil, anthracene oil, lubricating and fuel oils, greases, creosote, lamp black, benzol and its derivatives.
     Aliphatic compounds.
   - B. Inorganic chemicals
     Arsenicals, chromates, and crude sodium nitrate.
2. Physical carcinogens
   Ultraviolet rays, corpuscular rays (alpha and beta rays), electronic rays (gamma rays, roentgen rays).

Table II

EXPERIMENTAL PRODUCTION OF SKIN CANCER

Agent	Success	Failure
Soot	Rabbit, mouse	
Arsenicals	Mouse,* hairless rat*	Rabbit, rat
Paraffin oil	Mouse	
Shale oil	Mouse	
Pitch and tar	Mouse, rat, rabbit, dog	Monkey
Crude oils	Mouse	
Ultraviolet rays (sun)	Rat, mouse	Rabbit
Roentgen rays	Rabbit, mouse, rat	
Anthracene oil	Mouse	
Radioactive substances	Mouse, rabbit	
Lubricating oils (some)	Mouse	
Creosote	Mouse	

* Controversial

Table III

INDUSTRIAL ENVIRONMENTAL CARCINOGENS

Name	Date	Discoverer
Soot	1775	Pott
Arsenic	1820	Ayrton
Petroleum oil	1875	Volkmann
Shale oil	1876	Bell
Pitch and coal tar	1876	Manouvriez
Crude oils	1879	Härting and Hesse
Sun (ultraviolet)	1893	Unna
Roentgen rays	1902	Frieben and Albers-Schönberg
Radium (leukemia)	1911	von Jagić, Schwarz, and von Siebenrock
Anthracene oil	1913	Rambousek
Radium (skin)	1920	Leitch and Sequeira
Lubricating oils	1922	Southam and Wilson
Creosote	1924	Cookson
Benzol (leukemia)	1928	Delore and Bergamo

Tar Cancer

In a broad sense tar is the residue of the destructive distillation of any organic matter. It includes four types of material, related to each other only in respect to their vegetable origin; namely coal tar, wood tar, bituminous shale tar, and petroleum tar, or crude oil. The carcinogenic chemicals of coal tar are found in that fraction distilled between 250 and 350° C, and in the carbon-pitch residue, which constitutes approximately 60 per cent by weight of crude tar. This carcinogenic fraction includes, besides pitch, the heavy and anthracene oils. Anthracene itself is not carcinogenic although many chemicals in this fraction, structurally similar, are potent carcinogens in laboratory animals. Here again it must be emphasized that results in laboratory animals are not necessarily indicative of response of humans; particularly while the inunction of pitch and tar has resulted in carcinoma in the mouse, rat, and dog, attempts to cause it in the monkey have been repeatedly unsuccessful.

The most important of the chemical compounds in tar responsible for cutaneous cancer after prolonged contact are

3,4 benzpyrene
1,2,5,6 dibenzanthracene
20 methylcholanthrene
9,10 dimethyl–1,2 benzanthracene
5,9,10 trimethyl–1,2 benzanthracene
phenanthrene

The earliest reference to tar as an industrial hazard is generally credited to Volkmann, who, in 1875, described the varied cutaneous lesions in those working with it as follows: "In an elderly working man I counted as many as fifteen large, hard, wart-like growths bordered with thick rinds, on the dark-brown flecked, fissured forearms, and three on the scrotum." Volkmann likewise emphasized the frequency of cancer on scrotal skin previously exposed to tar, petroleum oils, soot, and allied substances. He was probably the first to define the relationship between tar dermatergoses and carcinogenesis.

Schwartz and Tulipan mention the occurrence of epithelioma in five out of 100 workers employed in the manufacture of electric equipment. Although Schwartz, Tulipan, and Peck reported numerous instances of creosote burns in workers impregnating railroad ties with creosote, no case of creosote cancer of the skin has been recorded in the United States.

Bituminous Shale

Next to coal tar, shale is the most important source of tar responsible for industrial cancer of the skin. The responsible chemicals are similar in both; the most likely culprit being 3,4 benzpyrene. It is possible to obtain diesel oil, fuel oil, lubricating oil, kerosene, and gasoline from shale oil.

Petroleum Tar (crude oil)

The first reports of oil epithelioma[7] were those occurring in mule spinners and machinists in England. Not all petroleum oils are carcinogenic to equal degree. Those from Venezuela and Romania head the list while Pennsylvania and Russian oils are least carcinogenic. They seem to act by giving rise to a proliferative folliculitis, especially in those who are careless about their personal hygiene and have oily, seborrheic skins with a tendency to acne, comedones, and papillomas. This type of cancer has been reported in recent years on the hands and forearms of grease-pit workers in service stations and employees of oil refineries. Wood-tar and wood-pitch cancers of the skin are rare and not an industrial problem.

Benzol

The responsibility of benzol in causing leukemia due to its toxic effects on bone marrow was recognized in 1918.[6] The widespread exposure of workmen to benzol is evident from the many reports of benzol poisoning in recent literature. It is also significant that benzol has been demonstrated in the bone marrow of victims of chronic benzol poisoning from thirteen to twenty months after exposure to this chemical. It is also thought that chronic benzol poisoning may be responsible for some cases of polycythemia vera. Experimental evidence indicates that coal tar is also capable of eliciting leukemic reactions in mice.

Arsenic

For many years arsenic has played a doubtful role as a carcinogen, although next to soot it is the oldest substance related to the development of occupational cancer, having been so mentioned in 1820.

In 1815, scrotal cancers in arsenic and lead workers were attributed to environmental contact.[11] In 1944, scrotal cancer, in a number of Sardinian workers who used a spray containing sodium arsenate for combatting grasshoppers, was attributed to contact of the metal with the skin. It has also been recently reported in lead workers and silver miners, smelters, cotton-field workers, loaders and packers of arsenicals, vineyard workers, and workers in arsenic plants. However, since arsenic may be inhaled readily in dusts and is absorbable percutaneously, it is quite likely that industrial cancer of the skin is a result of systemic intoxication, depository or excretory contact

rather than a result of exogenous contact.

Wile is of the opinion that some other predisposing factors are essential, basing his opinion on the rare development of hyperkeratoses and cancer in persons exposed to arsenicals, none among 12,321 orchardists known to be in contact with lead arsenate, and none among the arsenic-eating mountaineers of Tyrol and Styria.

Downing states: "As regards cancer from arsenic, I have had several outdoor workers, especially those who spray arsenic compounds, who had on their hands numerous keratoses, the precursor of cancer." However, there is no evidence that the arsenic was responsible to the exclusion of sunlight.

Most investigators now agree with Schwartz that contact of arsenicals with the skin does not cause cutaneous cancer, but that ingestion or inhalation of these substances is essential. Experimentally, the administration of arsenic to mice and other small animals has not resulted in cancer, but then the relatively short life span may have prevented the metal from taking effect; or the more rapid and effective excretion of arsenicals through the hair in furred animals may be responsible for unsatisfactory experimental results. During the past fifteen years I have been unable to find a single proved instance of skin cancer due to contact with arsenicals in the United States.

Physical Environmental Carcinogens

Ultraviolet Rays

The carcinogenic action of the ultraviolet spectrum of solar radiation has been appreciated for many years. Unna in 1893 was among the first to emphasize its importance.

Since not only chronic solar or chemical dermatitis and cancer, but also the so-called senile keratoses, are absent or very rare in Negroes, it is probable that these precursors of cutaneous cancer in white persons are at least in part the result of exposure to environmental influences which are injurious.

The actual causative mechanism of solar cancer is obscure. It is improbable that neoplastic reactions ensue from a sudden, physically induced cellular mutation, because of the long latent period usually observed. Whether or not the photochemical production of endogenous carcinogenic chemicals through a direct action of ultraviolet rays upon certain cellular components (sterols, aromatic proteins, etc.) might be responsible is still uncertain. The prevalence of solar cancer on the face in comparison with its incidence on the forearms and hands of persons in whom these areas are all equally exposed to the sun may be explained on the basis that the higher cholesterol content of sebum on the face is a contributory carcinogenic factor.

Roffo, of the Cancer Institute of Buenos Aires, places much of the responsibility for epithelioma of the skin on actinic solar radiation. He believes that all cases are preceded by some hyperkeratosis which is dependent on several factors—the living cell, a sensitizing photodynamic substance, the presence of oxygen, and the rays of the sun. In animal experimentation he found the most potent wave lengths from 1800 to 3400 Å. In both animals and humans he also found an abnormally high cholesterol content of the skin before the development of tumors. Further research is needed to determine whether this is a reaction normally occurring under the influence of actinic rays or whether it reflects a constitutional tendency to some abnormality in lipid metabolism. While the ultraviolet rays are mainly responsible it is thought by some investigators that the visible spectrum may also be injurious.

Blum does not take a serious view of solar cancer in that under the most severe conditions of exposure, only 0.2 per cent of the population develop skin cancers. However, this type of malignant disease is important in industries where photosensitizing agents contact the skin, especially coal-tar derivatives. It is interesting that carcinogenic tar fractions fluoresce and have specific fluorescence spectra. The absorption spectra of anthracene and acridine occur predominantly at 3200 and

3800 Å. Spectral bands at 2544 and 3640 Å are shown by 1,2 benzpyrene.

The importance of sunlight in skin cancer is significantly demonstrated when we review the incidence as compared with the intensity and duration of sunlight in various cities (Table IV).

Table IV

RELATION OF INTENSITY OF SUNLIGHT TO SKIN CANCERS

Epithelioma per 100,000 Population	City	Per Cent Sunlight
140	Dallas	60 - 80
129	New Orleans	62 - 64
37	Pittsburgh	50 - 57
24	Detroit	40 - 45

Radioactive Substances

With the extensive military and civilian use of atomic energy and the numerous radioactive fission products, plutonium, radiostrontium, and many others, radiation cancer has achieved considerable importance. For almost a half century the danger of cancer from roentgen rays and radium was confined to a relatively small group in the scientific field and to those physicians using these modalities. But despite all kinds of improvements in roentgen apparatus and safety devices many injuries are still caused by radiation. Even today physicians are careless, many unknowingly so. Dentists and roentgen-ray technicians working in dentists' offices are often exposed to sufficient scattered radiation to cause blood and marrow changes.

The indiscriminate use of electronic energy in World War I resulted in many burns with frequent carcinomatous sequelae, which follow approximately 25 per cent of all cases of chronic radiodermatitis.

Despite our smugness that we are thoroughly familiar with the dangers of electronic and corpuscular energy, its industrial use in the more recent wars has not been entirely free of similar complications both in hospitals and in shipyards where it was used for inspection of castings and weldings. In recent years there has been a significant increase in the use of the roentgen ray in industry. It is used in some states for fluoroscopy in shoe stores, in shoe factories to detect misplaced nails in shoes, as a means of detecting foreign bodies in any packaged goods, including foods, and in the manufacture of plastics and the like. It is also used effectively in the U. S. Customs Service to detect contraband and concealed dutiable articles. Radium-coated bars are used as static eliminators to prevent fire hazards in printing houses.

Thermic Cancer

The development of cancer, predominantly of the squamous-cell type in scars of old burns and accidental wounds, especially when these are extensive and contractile, is common, although the exact mechanism is obscure. Definite proof is not obtainable, however, that thermic burns, per se, either acute or chronic, are actually causative. Heat waves carry a relatively small quantity of energy so it is unlikely that they would so influence the chemical structure of a cell as to give birth to endogenous carcinogens such as follow exposure to ionizing types of radiant energy.

It is also the consensus that thermic radiation acting over long periods is not carcinogenic, although there are several cases in which this pathogenesis was proposed. The most notable one was the development of cutaneous cancer on the shins of English railroad engineers, allegedly caused by heat of the firebox. Undoubtedly these cases were due to carbon soot, and oil. Another was the development of a cancer on the face of a fair-skinned, red-haired man employed in a rolling mill where he was exposed to excessive radiant heat. This was merely a coincidence; and the fact must not be disregarded that most people exposed to excessive radiant heat are also usually in contact with coal or oil.

Trauma

No environmental influence has caused as much of a problem as mechanical or physical trauma as a contributing cause of cancer. Until a specific exciting cause is known the problem will never be solved. In determination of the role of trauma in causing a skin lesion there is an important personal element which requires interpretation by one well-versed in the vagaries of the human psyche. Fortunately, claims for skin cancer based on a single mechanical trauma are rarely encountered. When one thinks of the many minor abrasions, erosions, and bruises usually held responsible for epithelioma one appreciates the improbability of traumatic etiology.

In order to attribute cancer to a single injury certain requisites must exist: (1) There must be concrete evidence that the involved area or areas were previously normal. (2) There must be corroborative evidence of the injury and its exact site. It is characteristic of human nature that when a defect occurs in the skin, the individual reflects as to the cause. The chances of recollecting an injury in the neighborhood of the lesion are quite good. Maybe the injury was only a few inches away; but as the individual thinks the matter over, the site of trauma moves closer and closer to the site of the lesion until eventually he is honestly convinced that the lesion marks the exact site of the trauma of long ago. (3) There must have elapsed a sufficient time lag period between the alleged injury and the appearance of the cancer. (4) Clinical and histological diagnosis of the tumor must be made.

Ewing, who made a special study of trauma and cancer, was adamant in the belief that a single mechanical trauma to normal tissue was not responsible for malignant change. However, he did admit it to be an important indirect determining cause of certain tumors; but in such cases he found that additional factors, such as delayed healing, infection, chronic irritation, and probably hereditary and local predisposition were largely contributory. Production of tumors in experimental animals by trauma occurs only under special conditions of inherited or induced susceptibility, quite without parallel in man.

On the contrary, many physical and chemical injuries, such as contusions, lacerations and burns, acting on skin previously exposed to known carcinogenic contactants, may initiate sudden and rapid growth of cancer in the injured tissue. Likewise traumatization of cutaneous cancer may accelerate its growth or be responsible for its metastasis. Nor need this trauma be other than mild in nature, such as simple friction or pinching. In like manner, trauma to normal skin, remote from the site of a cutaneous cancer, may create a new area favorable to development of metastatic lesions.

Conclusion

In control of industrial cancer a fertile field exists, inviting the cooperation of government, management, and labor. It is fortunate that no other major industrial country is as remiss and negligent as we are in legislation and in administration of laws and ordinances for correction of abuses in industry predisposing to cancer of the skin.

References to articles mentioned are available upon request. Address:
Mr. Russell Gray Smith
Distribution Manager
American Cancer Society, Inc.
521 West 57 Street
New York 19, New York

Keratoacanthoma

Morris M. Cohen, M.D.

Keratoacanthoma is a benign tumor of the skin which the general practitioner, surgeon, and general pathologist should be acquainted with. This tumor is known and recognized by the dermatologist and dermohistopathologist. Keratoacanthoma has been mistaken both clinically and histologically for a prickle-cell epithelioma of the skin with the result that radical surgery and unnecessary, large doses of roentgen ray have been administered to these benign lesions. It is also important that the pathologist be familiar with this tumor to be able to recognize and interpret the findings under the microscope.

Keratoacanthoma, which is also known as molluscum sebaceum, may occur either as a solitary single lesion or may be multiple. The usual sites are the exposed areas of the body—the face and dorsal surfaces of the hands and forearms. An important diagnostic point clinically is that these lesions arise rapidly, usually within a four- to six-week period. This time factor is important in differentiating it from a prickle-cell epithelioma where the development and course cover a longer period of time.

Clinically, a keratoacanthoma shows the following features: It may measure from 1 to 2 cm. in diameter and appear as a round, elevated, nodular growth or as a button-like tumor showing central umbilication. The center of the lesion is keratotic and filled with a keratinous plug which is another clinical differential feature. Its rapid development in a period of several weeks is again emphasized.

Many theories have been advocated as to the etiological agent responsible for the origin of these tumors. A virus is believed by some to be the causative factor, while others feel that exposure of the hands and arms to lubricating oils and tar compounds may be responsible in those individuals in the industrial field. Trauma, lacerations, burns, and exposure to actinic rays are some additional factors suggested as the responsible and causative agents.

These benign lesions may be treated by simple surgical excision or by electrosurgery and curettage. They do not metastasize and do not show any regional adenopathy. If they are multiple, those that are untreated may heal spontaneously in six to twelve months. Certainly, a single keratoacanthoma should always be submitted to biopsy examination and the pathologist should be informed and acquainted with the clinical description of the lesion, its duration, etc. If these facts are not known to him, the interpretation of a prickle-cell epithelioma may be erroneously submitted as the microscopic diagnosis.

From the Divisions of Dermatology, University of Maryland School of Medicine and Johns Hopkins University School of Medicine, and Baltimore City Health Department.

Books of Current Interest

OCCUPATIONAL DISEASES OF THE SKIN, 3d ed. By Louis Schwartz, M.D., Louis Tulipan, M.D., and Donald J. Birmingham, M.D. Philadelphia. Lea & Febiger. 1957. 981 pages with 191 illustrations. $18.00.

PHYSIOLOGY AND BIOCHEMISTRY OF THE SKIN. By Stephen Rothman, M.D., Professor of Dermatology, University of Chicago, Chicago [with contributions by others]. University of Chicago Committee on Publications in Biology and Medicine. Chicago. University of Chicago Press. 1954. 741 pages. Illustrated. $19.50.

CANCER CLINIC

Cancer of the Skin

Conference of the Sections on Dermatology, Radiology, Plastic Surgery, and Pathology of the Lovelace Clinic, Albuquerque, New Mexico.*

Today we have two patients who were referred for suspected cancer of the skin. During the discussion we will consider the symptoms and findings which suggest skin cancer to the examining physician. Procedures necessary to establish a definitive diagnosis of skin cancer will be outlined. The epidemiology of malignant skin change is particularly relevant in both of these cases. Basic skin type, climate, and occupational or avocational exposure all play a part. Finally, we shall review the rationale for treatment in each case.

Case 1. A 70-year-old, fair-skinned, blue-eyed, semi-retired rancher was born in southwestern Texas and has spent all of his life in the Southwest, chiefly in southern New Mexico as cowboy and rancher. From his earliest youth he recalls many repeated episodes of severe sunburn and has lived a constant outdoor life. For the past ten or more years he has noticed patches of dry, rough, recurrent scaling on the face, neck, and backs of the hands. During the past three years an area in the skin over the right zygoma has shown progressive crusting, erosion, ulceration, and nodular infiltration (Fig. 1). On the dorsum of the right hand a horn-like growth has developed slowly (Fig. 2). This area has recently bled easily on slight trauma, and the patient describes a slowly enlarging, red, elevated, tender zone at the base of the horn.

Examination reveals widespread changes in the skin of the face, neck, ears, and backs of the hands. There are irregular areas of hyperkeratosis, scaling, crusting, and erosion. Other patches show telangiectasis, atrophy, and mottled hyper- and hypopigmentation. Over the right zygomatic prominence is an infiltrative, irregularly nodular growth with a pearly margin. The center is ulcerated with a loosely adherent serosanguineous crust.

*John C. Murphy, M.D., Dermatology; Jack W. Grossman, M.D., Radiology; Joseph G. Riley, M.D., Plastic Surgery; and Birdsall N. Carle, M.D., Pathology.

Just below the tumor there is an irregular, dark-brown, verrucoid patch. On the dorsum of the right hand, in addition to the extensive changes of "ranchers' skin" ("sailors' and farmers' skin"), there is a hard, horny protuberance. At its base is a red, elevated, ring-like area of infiltration with thin epithelial covering.

Case II. A 22-year-old medical student who has red-blond hair, blue eyes, and freckles was born in Oklahoma and has lived all of his life in the Southwest. Outdoor activities, including farm life, golf, swimming, and fishing have resulted in many episodes of severe sunburn as well as continuous excessive exposure to sunlight. For the past two years he has been aware of a small, firm papule just below the left eye (Fig. 3). This nodule has grown very slowly but there have been no other symptoms.

Examination reveals a milk-white skin sprinkled with orange freckles. Below the left eye is a sharply circumscribed, waxy, oval tumor with thin, tight, epithelial covering in which appear many fine capillary vessels.

Diagnosis. Clinically, Case I shows extensive signs of actinic damage. On the right cheek is an ulcerated tumor typical of basal-cell carcinoma. In addition, a dark-brown, verrucoid area suggests seborrheic keratosis. Below the eye can be seen irregular, rough, hyperkeratotic, actinic ("senile") keratoses. The lower lip shows the dry, white, thickened changes of early leukoplakia. On the dorsum of the right hand there is a cutaneous horn with infiltrative activity at its base. To establish specific diagnosis of each lesion, pathologic study of the tissues was made. Punch biopsy was made of each lesion on the face. The cutaneous horn, with a surrounding area of normal tissue at its base, was excised by electrosurgery. Histologic study showed the brown wart-like area on the face to be a seborrheic keratosis. The ulcerated tumor of the face was a basal-cell carcinoma. The specimen from the hand revealed cornu cutaneum with early malignant epidermoid (squamous-cell) changes at the base.

In Case II, microscopic study of a punch biopsy demonstrated a compact growth of basal-cell tumor.

Treatment. Seborrheic keratoses, which only rarely become malignant, and actinic keratoses also, are most satisfactorily treated with electrocoagulation. The dark-brown, verrucoid area and the actinic keratoses on the face in Case I were removed in three separate stages under local procaine anesthesia. The basal-cell tumor in Case I was treated with roentgen rays. Three equal doses were given at weekly intervals using the factors: Quality of radiation HVL 2.8 mm. Al, 100 KVP, 2.5 mm. Al filtration, 25 cm. FSD, for a total of 3660 r. Careful study of sections from the edges of the excised cutaneous horn and its epidermoid carcinoma indicated adequate primary excision with electrosurgery. The same result would have followed wide surgical excision and suture. Either procedure is considered better than roentgen rays for this kind of lesion on the dorsum of the hand. Periodic examination for two years has shown no evidence of recurrence in any of the areas treated.

After consultation in all departments it was agreed that the most appropriate treatment for the basal-cell tumor in Case II would be surgical excision. The area was removed to include a rim of normal tissue with an elliptical incision and primary closure. Microscopic study of the specimen showed an adequate margin beyond the tumor in all directions.

Etiology. Both of today's cases of skin cancer demonstrate forcibly the roles of three well-known carcinogenic factors in producing malignant skin degeneration. Fair-skinned people, especially those with blue eyes and red hair, who have little or no inherent pigment-forming ability, are more susceptible to skin cancer. The ultraviolet rays of sunshine not only burn and tan but, in time, may stimulate neoplastic changes in human skin. Repeated exposure to irritants, chemical or physical, increases the incidence of cancer.

Each of our patients is of the blond-skin type most susceptible to actinic damage. Each has lived in a geographical area where total sunshine and percentage of

Fig. 1. Generalized actinic damage of face with basal-cell tumor and seborrheic keratosis of cheek. Actinic ("senile") keratoses under eye and leukoplakia of lip.

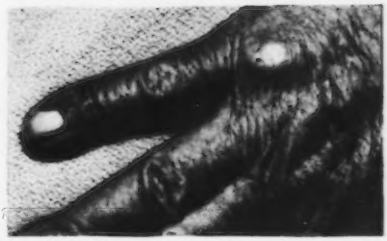


Fig. 2. "Ranchers' skin" and cutaneous horn at base of little finger.

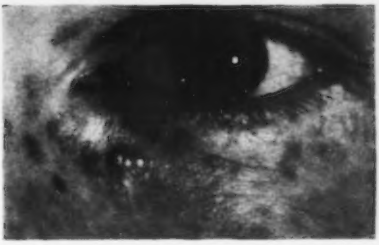


Fig. 3. Basal-cell tumor below eye.

ultraviolet ray are most intense. Each has engaged in outdoor activities resulting in frequent and repeated exposure to the persistent sunshine of the Southwest.

The case of the elderly rancher is less remarkable than that of the young student. A long life of outdoor work resulted in prolonged exposure to actinic rays. But to find a typical basal-cell tumor in a man of twenty-two is less expected. In the Southwest, however, we not infrequently see malignant skin changes in quite young people. Such lesions should not be minimized clinically simply on the basis of age. Nor are the damaging effects of continuous sunlight limited only to those with blond skin. Repeated actinic exposure can produce skin cancer in brunette and even dark-skinned persons if sufficiently prolonged and repeated. Every lesion on exposed areas must be suspected. Examination for definitive diagnosis, including biopsy if there is any possible doubt, should be made to establish a specific diagnosis and to determine the appropriate treatment.

References to Neoplasms of the Skin in Previous Issues of CA

2:192, Nov., 1952	Carcinoma of the skin.
2:195, Nov., 1952	Industrial aspects of cancer of the skin.
2:199, Nov., 1952	Precancers of the skin: their recognition and management.
2:207, Nov., 1952	Cancer clinic.
3:73, March, 1953	Influence of sunlight on skin carcinogenesis.
3:131, July, 1953	Leukoplakia.
7:18, Jan., 1957	Cancers related to custom, occupation, and environment.

new developments in cancer

Styrylquinolines . . .

Another experimental tumor, Walker 256, has been added to the conquests of styrylquinolines synthesized by Dr. Carl Tabb Bahner of Carson-Newman College and tested by Dr. Margaret Reed Lewis of the Wistar Institute and Dr. Boland Hughes of the University of Pennsylvania. Tumors in rats receiving a styrylquinoline in their diet one day after implantation were one-tenth as large as tumors in the untreated controls at the end of fifteen days. Toxic effects included a depressed white-cell count and sometimes reduction of hemoglobin. Delay in administration also weakened the therapeutic effect. In earlier tests, styrylquinolines given in the diet completely destroyed some transplanted lymphomas. In other kinds of experimental cancers the drugs were less effective or completely ineffective.

Actinomycin D . . .

There's always that one case . . . Dr. George E. Moore and others of Roswell Park Memorial Institute have reported that a man with advanced stomach cancer responded dramatically but temporarily to actinomycin D. Metastases shrank and circulating tumor cells were cleared out of the blood. Relatively minor effects were observed in thirty-one other patients, about one-third of whom developed stomatitis and alopecia.

On the Brighter Side . . .

Scientists at the National Cancer Institute have reported favorable results with antifolic and antipurine compounds against human trophoblastic cancers. The patients were treated with methotrexate, and sometimes 6-mercaptopurine, under a dosage regimen for about two months. Results: Two women with choriocarcinoma and one with chorioadenoma showed regression of metastatic tumors and other objective signs of remission twelve to seventeen months following methotrexate therapy. Two have had no detectable cancer for more than one year. Three men with embryonal tumors of the testis had a brief one and one-half to two months remission with methotrexate, and one has obtained a second remission with 6-mercaptopurine. The scientists are Drs. Min Chiu Li, Donald B. Spencer, Roy Hertz, and Herbert A. Lubs.

Bernfeld and Nisselbaum (Tufts) have found that as tumors grow, new plasma α-globulins appear and the normal α-globulin proteins disappear.

Liebelt (Baylor) induced obesity in male and female mice and found hepatomas in 73 per cent of the fat males, 6 per cent of the non-obese males, 17 per cent of the fat females and 0 per cent of the non-obese females. Testicular or adrenocortical androgens appeared to be necessary for tumor development.

Krementz, Pang, and Couch (Tulane) concluded from rabbit experiments that placenta effectively bars blood-borne metastases. The conclusion was based on close study of mother and fetal rabbits, the mothers having been injected with Brown-Pearce tumor cells when 13 to 16 days pregnant.

Haddow and others (Chester Beatty, London) reported that breast xanthine oxidase, which increases in pregnancy, was depressed to 58 per cent normal in breast cells of cancer-susceptible but non-tumor-bearing mice and to 25 per cent in breast cells of those with spontaneous mammary tumors.

Kapnick (Miriam Hospital, Providence) has decided that spinal-fluid acid phosphatase is an excellent indication of early metastatic carcinoma of the spine. He tested the spinal fluid of 344 cancer patients for acid or alkaline phosphatase.

Kit and Graham (M. D. Anderson), using Kit's remarkable methods of biochemical analysis, have traced the incorporation of glucose-C^{14} into RNA pentose by lymphatic tissues and tumors. Two pathways were tested: 1) the direct oxidative, and 2) the transketolase-transaldolase routes. Conclusion: "A substantial proportion of RNA pentose is formed via the transketolase-transaldolase pathway in each of the tissues."

Homburger, Borges, and Tregier (Tufts) reported producing morphologically malignant sarcomas in the myometrium of mice with ligated uterine cervixes (resulting in hydrometra) and treated with testosterone. Tumorigenesis followed the administration of testosterone in seven days.

Metcalf (Children's Cancer Research Found.) has confirmed the role of the thymus in regulating lymphocyte levels and has shown that in high-leukemic mice thymal overactivity is present from birth. Thymus emulsions produced a lymphocytosis in low-leukemic strains but did not

elevate further the high lymphocyte levels in leukemic-prone animals. This basic finding is of importance in tracing leukemogenesis -- lack of appreciation of the thymus role in health and disease has frustrated many investigators.

Weinhouse and Bloch-Frankenthal (Lankenau) observed marked inhibition of oxygen consumption by ascites-tumor cells in the presence of high glucose concentrations -- but this was not accompanied by an inhibited glucose oxidation. The effect was exerted on an endogenous (probably fatty acid) respiration.

The Ambruses, Feltz, and Wenner (Roswell Park) have failed to confirm reports of radioprotection afforded by adrenochrome derivatives and chlorpromazine in tests on several solid, systemic, transplanted, and spontaneous tumors in mice. They reported also that marrow, spleen suspensions, and lymph administered after irradiation were not superior to selective irradiation and shielding and did not add to the safety of shielding. The failure of thyroxin to increase oxygen uptake by neoplastic transplants (and thus increase their vulnerability to X rays) was interpreted this way: Normal tissues increase their oxygen uptake more than malignant tissues do; and at the same time methemoglobin formation produces relatively greater anoxia in normal tissues.

Chang, Spain, and Griffin (M. D. Anderson) serially examined the livers of rats on a 3'-Me-DAB diet. First seven days: No change. Starting with fourteen days, however, there was a consistent depletion of glycogen, esterase, RNA, and mitochondria and an increase in alkaline phosphatase.

Conney and J. A. Miller (U. of Wis.) have observed that the detoxifying activity of benzpyrene hydroxylase increases 5 to 10 times in twenty-four hours after the parenteral injection of benzpyrene and related hydrocarbons. Ethionine completely prevented an increase in this liver enzyme's activity -- and methionine abolished the ethionine effect. Earlier experiments showed that carcinogenic hydrocarbon injections destroy the carcinogenicity of azo dyes, probably by similar enzymes which remove the methyl group and reduce the azo linkage. J. A. and E. C. Miller and Gelboin have shown that dietary protein is necessary for the synthesis of the cancer-preventing azo dye-binding liver proteins.

COMING MEDICAL MEETINGS

Date	Meeting	City
1957		
Dec. 7	Cancer Seminar, Oklahoma Division, American Cancer Society, Inc.	Oklahoma City
Dec. 7-12	American Academy of Dermatology and Syphilology	Chicago
Dec. 26-30	American Association for the Advancement of Science	Chicago
1958		
Jan. 22	Mississippi Academy of General Practice	Jackson
Jan. 23-25	Cancer Seminar, Arizona Division, American Cancer Society, Inc.	Tucson
Feb. 5-8	American College of Radiology	Chicago
Feb. 17-19	Atlanta Graduate Medical Assembly	Atlanta
April 27-May 1	Society of American Bacteriologists	Chicago
April 28-30	Tri-State Hospital Assembly	Chicago
April 28-May 1	American Urological Association	New Orleans
April 28-May 2	American College of Physicians	Atlantic City
May 2-4	Student American Medical Association	Chicago
May 5	American Society for Clinical Investigation	Atlantic City
May 8-9	American Pediatric Society	Atlantic City
May 8-11	Virginia Academy of General Practice	Virginia Beach
May 13-15	Mississippi State Medical Association	Jackson
May 16-18	American Association for Thoracic Surgery	Boston
May 17-18	American Otological Society	San Francisco
May 19-20	American Laryngological Association	San Francisco
May 19-21	American Gynecological Society	Asheville
May 19-23	American Trudeau Society	Philadelphia
May 19-24	National Tuberculosis Association	Philadelphia
May 20-22	New England Postgraduate Assembly	Boston
May 20-24	American College of Cardiology	St. Louis
May 21-23	American Laryngological, Rhinological and Otological Society	San Francisco
May 21-23	American Broncho-Esophagological Association	San Francisco
May 21-23	Middle Atlantic Hospital Assembly	Atlantic City
May 25-31	World Congress of Gastroenterology	Washington, D. C.
May 30-31	American Gastroenterological Association	Washington, D. C.
June 4-8	American Dermatological Association	Sun Valley, Idaho
June 9-13	American Nurses' Association	Atlantic City
June 15-21	American Society of Medical Technologists	Milwaukee
June 16-18	American Neurological Association	Atlantic City
June 16-20	Canadian Medical Association	Halifax
June 18-22	American College of Chest Physicians	San Francisco
June 19-20	American Geriatrics Society	San Francisco
June 19-21	The Endocrine Society	San Francisco
June 19-22	American Medical Women's Association	San Francisco
June 21	American Academy of Tuberculosis Physicians	San Francisco
June 22-28	Congress of International Federation of Gynecology and Obstetrics	Montreal

324

PHOTOENGRAVINGS BY ROGERS ENGRAVING COMPANY, NEW YORK, NEW YORK
PRINTED IN THE UNITED STATES BY PACE PRESS, INC., NEW YORK, NEW YORK